Asthma, airway hyperresponsiveness and exposure to indoor allergens

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SUMMARY

Allergic sensitization to indoor allergens is an important risk factor for the development of asthma and exposure to these allergens is an important cause of asthmatic symptoms in sensitized patients. Recommendations for reduction this exposure are important in the treatment of allergic patients. During the last decade, specific assays for assessment of allergen exposure have become available and it has therefore become possible to evaluate the effects of allergen avoidance measures.

The aim of the studies documented in this thesis was to investigate the relationship between natural exposure to indoor allergens (house dust mites and pets) and symptoms and the degree of airway hyperresponsiveness (AHR) in asthmatic patients sensitized to these allergens. Furthermore, we studied the effects of some allergen avoidance measures on allergen levels in homes of sensitized asthmatic patients and on clinical symptoms as well.

In ***Chapter 2,*** the natural variation of house dust mite allergen levels in floor dust from living-rooms and bedrooms was analysed in houses of 9 adult asthmatic patients who were only sensitized to house dust mite allergens. After monthly collection of floor dust samples by vacuum-cleaning during one year, a seasonal variation in concentration of mite allergen (Der p 1) was observed with the highest concentration (▲Der p 1= + 2.31 μg/g compared to year average) during late summer-beginning of autumn, and relatively lower concentrations (▲Der p 1= - 1.33 μg/g) during the spring months (March - May). The seasonal changes in mite allergen levels were in agreement with the observed changes in absolute air humidity, with maximum humidity during the months July to September. The differences in house dust mite allergen concentration, however, were much greater than the observed seasonal changes.

During the same year, lung function (spirometry) and AHR, as estimated by the PC_{20} histamine, were also assessed monthly in the ten patients. Lung function did not change over the year, but AHR also showed a seasonal variation with less AHR during spring and increased AHR during late summer-begin of autumn (▲PC_{20}histamine = - 1.47 mg/ml during autumn and + 1.79 mg/ml in spring, both compared to year average). During the autumn period, the highest number of peripheral blood eosinophils were found. Our results suggest that in asthmatic patients with an isolated sensitization to house dust mites, small changes in exposure to mite allergens may be accompanied by small but statistically significant changes in AHR. The observed seasonal variations may differ, however, among years because of differences in climatic conditions (temperature, humidity, etc.) .

In order to evaluate the observed associations between seasonal changes in mite allergen concentrations and AHR, the study mentioned in chapter 2 was extended to a larger group of 43 asthmatic patients with sensitization to other inhalant allergens (pollen, cat and dog) as described in ***Chapter 3.*** Dust samples from floors were collected twice both during autumn and during spring. A seasonal variation in mite allergen levels in floor dust was found but the differences in mite allergen concentrations in floor dust between spring and autumn were smaller than found in the first study. As in the first study, a seasonal variation in AHR was again found with less AHR during spring and increased AHR in autumn. However, this seasonal variation of AHR was only observed in patients (n=32) sensitized to house dust mites with a PC_{20}histamine of 2.05 mg/ml for autumn and 4.51 mg/ml for spring ($p<0.01$). AHR in patients not sensitized to house dust mites was similar for both seasons. Also, serum IgE showed a seasonal variation in house dust mite sensitive patients and the number of peripheral blood eosinophils during autumn differed significantly between house dust mite sensitized and non-sensitized patients ($p<0.01$). Therefore, a seasonal change in AHR may be found in asthmatic patients who are sensitized to house dust mites.

Aside from sensitization to house dust mites, allergic (asthmatic) patients can also be sensitized to other mite species such as storage mites. In ***Chapter 4***, the degree of sensitization to three storage mites (*Acarus siro*, *Tyrophagus putrescentiae*, and *Lepidoglyphus destructor*) was studied in sera of patients with different degrees of sensitization to the house dust mite *Dermatophagoides pteronyssinus*. Sensitization to storage mites is clearly related to sensitization to *D.pteronyssinus*: in patients without sensitization to *D.pteronyssinus*, only 10% of the sera showed increased but low levels of IgE antibodies against at least one of the three storage mites. In sera with a high level of IgE against *D.pteronyssinus*, however, up to 70% of the sera contained IgE against at least one of the storage mites. However, the question is whether co-sensitization to storage mites is caused by co-exposure to storage mite allergens or by cross-reactivity between house dust mite and storage mite allergens. RAST-inhibition experiments demonstrated considerable allergenic cross-reactivity between the different mite species, especially between *A.siro* and *T.putrescentiae*. Furthermore, the allergens of the tree storage mites cross-react up to 60% with allergens of *D.pteronyssinus*. Therefore, co-sensitization to storage mites is common in allergic patients who are sensitized to *D.pteronyssinus*. A large part of this co-sensitization (up to 60%) can be attributed to allergenic cross-reactivity. However, co-sensitization due to co-exposure cannot be excluded, especially in people with a known domestic or professional exposure to storage mites. More information about specific exposure to storage mite allergens is needed. Thus part of the symptoms of house-dust mite allergic patients may be caused by exposure to other mites than *D.pteronyssinus*.

To further analyse the importance of exposure to house-dust mite allergens, in ***Chapter 5***, a study is described which investigated whether domestic exposure to house dust mite allergens can be reduced beneficially by application of a house dust mite killing chemical (an acaricide) on mattress and on carpets in living-rooms and bedrooms. The acaricide (or the placebo material) was applied at the start of the study and repeated after 6 months. The study was performed in a double-blind, placebo-controlled, parallel design, in the homes of 40 asthmatic patients sensitized to house dust mites. With a second group of 19 patients who refused a chemical intervention in their homes, the clinical effects of allergen-impermeable encasings were studied. Clinical changes were examined after 3, 6, and 12 months. The treatment of mattresses with an acaricide significantly reduced the concentration of the mite allergen Der p 1 in mattress dust after 12 months (4.5 μg/g to 1.9 μg/g, $p<0.01$). However, treatment of the mattress with a placebo agent (a common detergent) decreased the mite allergen in a similar way. The largest reduction of the mite allergen concentration in mattress dust was observed with mattress encasings. Furthermore, the residual mite allergen concentration in mattress dust after the use of an acaricide remained considerable (about 2 μg/g). Clinical benefit was detected by an improvement of airway hyperresponsiveness (increase of PC_{20} histamine) in patients after intervention with an acaricide ($p<0.05$) and after application of mattress encasings ($p<0.01$). Mattress encasings may play a beneficial role in asthmatic patients sensitized to house dust mites. Additionally, mattress encasings can be applied easily and the compliance of patients is high. The use of acaricides (or treatment with other chemicals) should be restricted to particular locations where better allergen reduction measures cannot be applied.

In ***Chapter 6***, a study is described in which effects were analysed of air cleaners placed in the living-rooms of adult asthmatic patients sensitized to house dust mites. We considered this to be another way to reduce exposure to house-dust mite allergens and than to test the clinical relevance of this measure. The study lasted 6 months and had a parallel, double-blind, placebo-controlled design. The air cleaners (active or sham air cleaners) were used with or without allergen-impermeable mattress encasings. The patients were divided in three groups. Group 1: intervention with active air cleaners alone, group 2: intervention with sham air cleaners and mattress encasings, and group 3: intervention with active air cleaners combined with mattress encasings. Although considerable amounts of house dust mite allergen Der p 1 were captured in the filters of the active air cleaners, no clinical changes were observed in Group 1 (active air cleaners only). In Group 2 (sham air cleaners combined with mattress encasings) a trend to improvement of AHR (PC_{20} histamine) was observed ($p=0.09$) whereas a statistically significant change in AHR was found in Group 3 (active air cleaners and mattress encasings). Our results suggest that clinical effects of air cleaners on asthmatic patients sensitized to house dust mites is limited. House dust mite allergens are mainly found

in large dust particles which settle rapidly and which become airborne only after disturbance of the air. Therefore, air cleaners are effective in decreasing exposure to house dust mite allergens substantially because most house dust mite allergens are present in reservoir dust in carpets, upholstered furniture and mattresses.

Chapter 7: In contrast to house-dust mite allergens, a substantial percentage (25%) of pet allergens (cat or dog) is found in small particles (aerodynamic diameter $\leq$ 5 μm) which can stay airborne for a prolonged time. From a theoretical point of view, air cleaners potentially should be able to reduce the concentration of airborne pet allergens. In order to obtain information about the importance of exposure to indoor allergens for asthma we studied the practical implications of the use of air cleaners in houses of asthmatic patients sensitized to cat or dog. The air cleaners were applied in the living-rooms and bedrooms of 20 asthmatic children sensitized to cat or dog and with animal exposure at home. The study was performed using a randomised, double-blind, placebo-controlled, crossover design.
After the use of (active) air cleaners during 3 months, AHR had been reduced substantially, as was demonstrated by an increase of 1.3 doubling doses in the PC_{20}-adenosine-monophosphate, whereas no changes were observed during the intervention with sham (placebo) air cleaners. Additionally, peak flow variation, expressed as amplitude percent of the mean, showed a small but statistically significant decrease only after use of active air cleaners. Up to 117 μg of cat allergen Fel d 1 and 265 μg of dog allergen Can f 1 were captured in the filters of active air cleaners. The captured amounts of cat and dog allergens correlated significantly with the concentration of these allergens in floor dust from living-rooms and bedrooms. The floor concentration did not change during the intervention with air cleaners. The results of this study show that application of air cleaners may be beneficial for asthmatic patients sensitized to pets, especially in persons who want to keep their pet. Whether air cleaners can help to reduce pet allergen exposure in public buildings (schools, day care centres, etc.) needs to be established.

In ***Chapter 8,*** the relation of mite allergy with lung function and airway hyperresponsiveness is reviewed. Sensitization to house dust mites (HDM) is very common in the atopic population and has been shown to be risk factor for the development of asthma and airway hyperresponsiveness (AHR). In a community-based study population in Norway, Omenaas *et al.* have shown that sensitization to HDM is a significant and independent risk factor for reduced lung function and Sherrill and co-workers in New Zealand found a lower Tiffeneau index in HDM sensitized children than non-sensitized children. In studies with asthmatic patients, however, the relation between mite sensitization and lung function is more complex, probably because of interference with other factors such as co-sensitization to other aeroallergens and medication use.

AHR is an important feature of asthma and the degree of AHR is easily altered after changes in allergen exposure in sensitized asthmatic patients (e.g. an increase in AHR after allergen inhalation-provocation in the hospital or a decrease of AHR in HDM sensitized asthmatics after a stay in the mountains). After the application of mite allergen avoidance measures, changes in AHR are more often detected than changes in lung function. The degree of AHR can be assessed by inhalation provocation with pharmacological stimuli such as histamine, methacholine and adenosine. Whether the different stimuli detect the same AHR or that different aspects of AHR are assayed by the diverse stimuli is not yet known.

GENERAL DISCUSSION

Allergen avoidance measures for secondary and tertiary prevention of allergic diseases

More than 75 years ago, it was already recognized that avoidance or reduction of exposure to indoor allergens may improve the clinical condition of sensitized asthmatic patients [1,2]. Most studies on allergy prevention have been performed to achieve tertiary prevention: the reduction of symptoms or improvement of lung function and/or airway hyperresponsiveness in sensitized asthmatic patients.

In 1927, Storm van Leeuwen observed a respectable degree of symptom reduction in asthmatic patients after a stay of two days in a so called allergen-proof chamber, which contained a smooth (hard) floor and a new mattress and bedding that had been sterilised [1]. Additionally, the room was mechanically ventilated using outdoor air. It is a sobering thought that many of our ideas about the relevance of allergen avoidance measures were already discussed in this paper.

Allergen avoidance measures may be beneficial for allergic patients in reducing allergic inflammation (airway hyperresponsiveness), symptom score or medication use. However, aside from the level of allergen exposure, the magnitude of the beneficial effect may depend on several cofactors such as individual patient characteristics (degree of symptoms, allergic sensitization pattern, medication consumption, etc.) and differences in environmental exposure (smooth or hard floors, smoking by co-residents, presence of pets, etc.). Many allergen avoidance measures and programs for tertiary prevention have been developed and recommended over the last decades [3-6]. In order to be beneficial for allergic patients, the following requirements of an allergen avoidance measure are formulated:

- causing a substantial reduction in allergen exposure
- clinically proven efficacy (reduction of symptoms, reduction in medication, etc.) against the specific allergen of interest
- effortless application of the measure

are probably beneficial but often difficult to realize. Such measures are also expensive and the effects often depend on outdoor climate [24].
Although the clinical relevance of mite-allergen avoidance measures has been questioned in a meta-analysis [25-27], anti-mite measures may play a beneficial role in the treatment of mite-allergic patients [3,4]

Avoidance of exposure to pet allergens

In the Western world, up to 65% of households keep furry pets [28,29]. In a prospective study of asthmatic children over a 30-year period, even 82% of the patients had a cat or dog at home in childhood [30]. The best measure for reduction of exposure to pet allergens is to remove the animal from the home, but many patients wish to keep their pet. Furthermore, after removal of the animal, it may take months before a substantial decrease of pet allergens in dust reservoirs within the home has occurred [31,32]. Washing of the cat or dog significantly reduces the amount of allergen which may be recovered from the animal but this must be repeated twice a week [33-35].
The use of air cleaners may be beneficial in allergic patients sensitized to pets and with the animals at home [4,36,37].
A special problem of exposure to pet allergens (especially from cat and dog) is the widespread presence of these allergens in public buildings such as schools, day care centres, hospitals, etc. [38-42]. Pet allergens are transferred on clothes from homes to schools and vice versa [42-45]. Exposure to these non-domestic allergen sources can negatively influence the effects of allergen avoidance measures at home [4,46].

Avoidance of exposure to mould allergens

Sensitization to moulds (particularly Alternaria and Cladosporium) is not uncommon in the allergic population, especially in children [47-50]. Additionally, sensitization to Alternaria has been shown to be an independent risk factor for the development of asthma and airway hyperresponsiveness in some areas of the world [51-53]. However, the relation between mould allergen exposure and subsequent allergic sensitization is difficult to establish, probably also because of the difficulty of a reproducible assessment of mould exposure [54-56]. A very recent paper offers a new possibility for the assessment of mould exposure by measuring the concentration of fungal extracellular polysaccharides in dust samples [57].
In several studies, reported home dampness was associated with sensitization to house dust mites and/or moulds [58,59]. Additionally, respiratory symptoms were associated with reported home dampness [57,60]. Until now, data from intervention studies for reduction of exposure to

mould allergens are not available. Whether (and which) health effects can be expected by reducing the dampness in homes is not known yet [61].

Avoidance of exposure to cockroach allergens

Cockroach allergens have been recognised in several studies as important inducers for allergic sensitization as well as being a risk factor for asthma in American inner-cities [62-64]. However, a high prevalence of sensitization to cockroach allergens was also found in Spain [65] and in China [66]. Aside from the kitchen, a considerable amount of cockroach allergen may be found in bedrooms [63]. Although chemical procedures are available for controlling cockroach growth, data about effects on sensitized patients is lacking.

Allergen avoidance in primary prevention of allergic diseases

The question of whether allergen avoidance during infancy can lead to a decrease in the incidence of allergic sensitization and allergic diseases in genetically susceptible children, has become an important issue during the last years and is currently the subject of several prospective birth cohort studies in different countries [67-70]. In a (relatively small) prospective birth-cohort study on the Isle of Wight, allergen avoidance measures (use of an acaricide in living-room and bedroom) were applied in combination with restriction of some food antigens in the mothers diet before and after birth and exclusive breast feeding during the first months, and the results were compared to a control group [71]. After 4 years, less total allergy, fewer positive skin test, and less eczema were found in the intervention group. Unfortunately, the difference in asthma prevalence, which existed at the age of one year between the intervention and the control group, had disappeared at the age of 2 years. However, it may be questioned whether the use of an acaricide is the most appropriate measure to reduce the exposure to house dust mites sufficiently [18,72,73].
In areas with very limited mite growth because of an exceptionally dry or cold climate, the sensitization to house dust mites is substantially lower than in control groups, but the prevalence of asthma is not necessarily lower in these areas and sensitization to other aeroallergens (cat, dog, birch, Alternaria or cockroach) may play a prominent role [24,48,74]. In Sweden, allergic sensitization to pets (cat and dog) but not to mites is an independent risk factor for asthma and airway hyperresponsiveness [75]. Therefore, allergen avoidance programs probably should consist of a combination of avoidance measures to reduce exposure to different common aeroallergens in such a way that primary prevention of allergic diseases by allergen avoidance might be a potential option. Even if it is possible to avoid allergic sensitization and development of allergic diseases by application of allergen avoidance

programs, an important question will be how to select children at risk. Although high-risk children (positive family history for atopy) have a greater chance of developing allergic disease, the majority of atopic manifestations (60%) is said to occur in infants with no demonstrable risk at birth [76].

During the last 3 decades, the prevalence of allergic diseases (asthma, hay fever, eczema) has increased considerably, especially in countries with a so called "Western" lifestyle [77-79]. Furthermore, the prevalence of asthma differs greatly between different countries or areas, even between areas with the same degree of atopy [80-83]. Although a small increase in allergen exposure may have occurred during the last decades because of energy savings programs, increased time spending indoors, and an increased use of wall to wall carpets, this increase is too small to explain the observed increase in asthma prevalence rates. Additionally, in some areas with a comparable allergen exposure, the prevalence of asthma differs among these areas [84,85]. Therefore, environmental factors other than allergen exposure must be responsible for the increased prevalence of allergic diseases [84-86]. Potential candidates are:

- family size (sibling effect)
- bedroom sharing
- parental smoking
- day care attendance
- contact with farm animals
- pet ownership in childhood
- diet
- maternal exposure to (food) allergens
- breastfeeding in relation to maternal allergy
- infections in infancy
- air pollution (indoor and outdoor)

Confusing data from studies has been published about a potential protective role of pet ownership in childhood on later development of atopy. In a birth-cohort study of Wahn *et al.*, a dose-response relationship was found between exposure to cat allergen and allergic sensitization to this allergen [87], indicating a greater sensitization risk at higher allergen exposure. Hesselmar *et al.*, however, found that children exposed to pets during the first year of life, had a lower frequency of allergic rhinitis at 7-9 years of age and of asthma at 12-13 years and children exposed to cat during the first year of life were less often SPT positive to cat at 12-13 years [88]. Similar results were found in the European Community Respiratory Health Survey (ECRHS) [89]. In a follow-up study of asthmatic children during 30 year, Grol *et al.* observed that having pets in childhood was associated with less severe airway hyperresponsiveness at age 32-42 year [30]. In childhood, however, no differences in severity

of airway hyperresponsiveness were found between children with or without pets. It has been proposed that a protective role for pet ownership in childhood on the development of allergic disease may be associated with increased exposure to microbial exposure due to pets [87]. Therefore, two effects of pet ownership may counteract on the development of allergic sensitization: a increased risk by higher allergen exposure versus a decreased risk by microbial exposure. Factors which are decisive in the direction of this process, have yet to be resolved. At last, a selective avoidance of pet allergen exposure during childhood in patients with most severe complaints may also influence the abovementioned relationships. Aside, from pet ownership, growing up in a farm environment during childhood may also reduce the risk of developing allergic diseases [90-92]. Although the mechanism of this farm protection has to be clarified, an increased exposure to bacterial compounds associated with farming, has been suggested as a explanation [90,91,93].

Much attention has been paid to the role of infections in early childhood which should protect genetically predisposed children for the development of atopy by promoting the maturation of a Th1-like immune response from the Th2-like response during fetal life [94-96]. Additionally, the observed protection of the presence of siblings and bedroom sharing on the development of allergic diseases could be explained by an increased load of infectious agents [97-100]. However, it is not clear at the moment whether modulation of the immune response by vaccination during infancy might act as protection against the development of atopy. Studies on this subject show conflicting results [101-105]. It is also possible, that the observed effects of vaccination might be explained by an inherited difference in immune response (maturational defect) of children with the atopic genotype as compared to control children [96]. The role of the infectious load in childhood (pathogens or perhaps, more important, probiotics present in the gastrointestinal and respiratory tract) in the development of atopic diseases in genetically predisposed children needs to be clarified. A reduced risk on hay fever and asthma by pet ownership or a farm environment in childhood may be mediated by an increased exposure to microbial agents. Future research must elucidate which combination of environmental risk factors (or the absence of these factors) are responsible for the increased prevalence of allergic diseases. It may be possible that adaptation of one or more factors can also be used for intervention programs to reduce the prevalence rates of allergic diseases. Whether allergen avoidance measures will be part of these programs has yet to be established.